PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 403/00 — A2

(11) International Publication Number: WO 00/35906

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/EP99/09578

(22) International Filing Date: 7 December 1999 (07.12.99)

(30) Priority Data:
60/112,589 17 December 1998 (17.12.98) US
60/141,482 29 June 1999 (29.06.99) US

(71) Applicant: F. HOFFMANN–LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH–4070 Basle (CH).

(72) Inventors: LUK, Kin–Chun; 66 Evergreen Drive, North Caldwell, NJ 07006–4622 (US). MAHANEY, Paige, E.; 243 Country Club Lane, Scotch Plains, NJ 07076 (US). MISCHKE, Steven, Gregory; Apartment F13, 565 Grove Street, Clifton, NJ 07013 (US).

(74) Agent: LOESCHNER, Thomas; Grenzacherstrasse 124, CH–4070 Basle (CH).

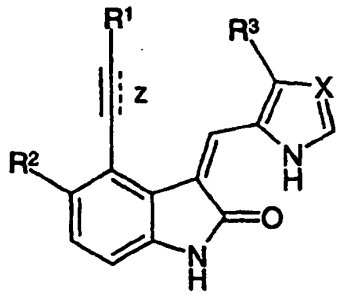
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: 4– AND 5–ALKYNYLOXINDOLES AND 4– AND 5–ALKENYLOXINDOLES

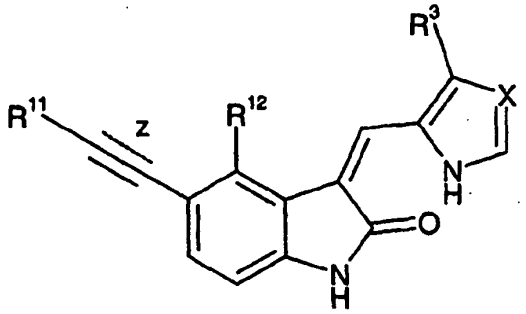
(57) Abstract

4– and 5–alkynyloxindoles as well as 4– and 5–alkenyloxindoles having formula (I) and (II), wherein R^1, R^2, R^3, R^{11}, R^{12}, X and z have the meaning indicated in the specification, inhibit or modulate protein kinases, in particular JNK protein kinases and are useful as anti–inflammatory agents, particularly in the treatment of rheumatoid arthritis.



(I)

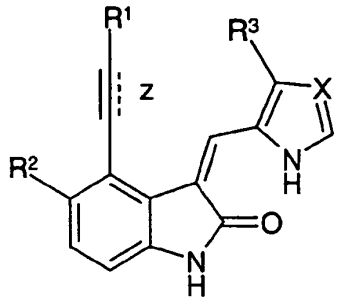
or



(II)

Claims

1. A compound having the formula



I

and the pharmaceutically acceptable salts thereof,

wherein:

R^1 is lower alkyl that is substituted by aryl, aryloxy, heteroaryl, heteroaryloxy, substituted aryl, substituted aryloxy, substituted heteroaryl, and/or substituted heteroaryloxy, and optionally also may be substituted by R^{13}, perfluoroalkyl, cycloalkyl (or cycloalkyl substituted by lower alkyl and/or R^{13}), or heterocycle (or heterocycle substituted by lower alkyl and/or R^{13}),

and wherein the substitutents on the substituted aryl, substituted aryloxy, substituted heteroaryl, and substituted heteroaryloxy are one or more of

R^{13}, lower alkyl (optionally substituted by R^{13}), cycloalkyl (optionally substituted by R^{13}), heterocycle (optionally substituted by R^{13}); aryl (optionally substituted by R^{13}, perfluoroalkyl, lower alkyl, lower alkyl substituted by R^{13}, cycloalkyl, cycloalkyl substituted by R^{13}, heterocycle (optionally substituted by R^{13}); or heteroaryl (optionally substituted by R^{13}, perfluoroalkyl, lower alkyl, lower alkyl substituted by R^{13}, cycloalkyl, cycloalkyl substituted by R^{13}, or heterocycle or heterocycle substituted by R^{13});

R^2 is hydrogen, $-OR^4$, $-OCOR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-NR^6R^7$, halogen, $-NO_2$, -CN, $-SO_2R^4$, $-SO_2NR^6R^7$, perfluoroalkyl, lower alkyl or lower alkyl substituted by $-OR^8$ or $-NR^6R^7$;

R^3 is hydrogen, $-OR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, halogen, -CN, $-NR^6R^7$, perfluoroalkyl, lower alkyl or lower alkyl substituted by $-OR^8$ or $-NR^6R^7$;

R^4 is hydrogen, lower alkyl (optionally substituted by (a), cycloalkyl and /or heterocycle), cycloalkyl (optionally substituted by (a), lower alkyl and/or heterocycle), heterocycle (optionally substituted by (a), lower alkyl and/or cycloalkyl), aryl (optionally substituted by (a), cycloalkyl, heterocycle and/or halogen), heteroaryl (optionally substituted by (a), cycloalkyl, heterocycle, and/or halogen,
where (a) is $-OR^5$, $-COOR^8$, $-COR^8$, $-CONR^8R^9$, $-NR^6R^7$, -CN, $-NO_2$, $-SO_2R^8$, and/or $-SO_2NR^8R^9$;

R^5 is hydrogen, $-COR^8$, $-CONR^8R^9$ or lower alkyl (optionally substituted by $-OR^9$, $-NR^9R^{10}$, $-N(COR^9)R^{10}$, $-COR^9$, $-CONR^9R^{10}$, $-SR^9$ and/or $-COOR^9$;

R^6 and R^7 are each hydrogen, $-COR^8$, $-COOR^8$, $-CONR^8R^9$, $-SO_2R^8$ $-SO_2NR^8R^9$, lower alkyl, lower alkyl substituted by (b), cycloalkyl (optionally substituted by (b), lower alkyl, and/or heterocycle), heterocycle, heterocycle substituted by (b), lower alkyl and/or cycloalkyl), aryl, aryl substituted by (b), lower alkyl, cycloalkyl and/or heterocycle), heteroaryl, heteroaryl substituted by (b), lower alkyl, cycloalkyl and/or heterocycle);

or R^6 and R^7 are each
cycloalkyl (optionally substituted by (b), lower alkyl and/or heterocycle; heterocycle (optionally substituted by (b), lower alkyl and/or cycloalkyl; aryl (optionally substituted by (b), lower alkyl, cycloalkyl and/or heterocycle; or heteroaryl (optionally substituted by (b), lower alkyl, cycloalkyl and/or heterocycle;
where (b) is OR^5, $-NR^8R^9$, $-COOR^8$, $-COR^8$, $-CONR^8R^9$, -CN, $-NO_2$, $-SO_2R^8$, $-SO_2NR^8R^9$;
alternatively, $-NR^6R^7$ can form a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms and being optionally substituted by one or more of lower alkyl, $-OR^5$, $-COR^8$, $-COOR^8$, $-CONR^8R^9$, and $-NR^5R^9$;

R^8 is hydrogen, lower alkyl (optionally substituted by cycloalkyl, heterocycle, aryl, heteroaryl, $-OR^9$, $-NR^9R^{10}$, and/or $-N(COR^9)R^{10}$),
aryl (optionally substituted by (c), lower alkyl, cycloalkyl and/or heterocycle),
heteroaryl (optionally substituted by (c), lower alkyl, cycloalkyl and/or heterocycle),
cycloalkyl (optionally substituted by (c), lower alkyl and/or heterocycle),
heterocycle (optionally substituted by (c), lower alkyl and/or cycloalkyl);
where (c) is $-OR^9$, $-COOR^9$, $-COR^9$, $-CONR^{10}R^9$, $-NR^{10}R^9$
$-CN$, $-NO_2$, $-SO_2R^9$, $-SO_2NR^{10}R^9$;

R^9 and R^{10} are each independently hydrogen or lower alkyl;

R^{13} is halogen, $-OR^4$, $-OCOR^4$, $-COR^4$ $-COOR^4$, $-CONR^6R^7$, $-NO_2$, $-NR^6R^7$, $-CN$, $-SO_2R^4$, or $-SO_2NR^6R^7$;

X is =N- or -CH-; and

the dotted bond represented by z is optional .

2. A compound of claim 1, wherein R^1 is

lower alkyl that is substituted by aryl or substituted aryl, and optionally also substituted by halogen, $-OR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, cycloalkyl, heterocycle, $-COOR^4$, $CONR^6R^7$, cycloalkyl which is substituted by OR^5, $-NR^6R^7$, $COOR^4$, $CONR^6R^7$, and/or heterocycle which is substituted by OR^5 and $-NR^6R^7$, $COOR^4$, $CONR^6R^7$; and wherein the substituents on the substituted aryl are selected from halogen, $-OR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-NO_2$, NR^6R^7, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, lower alkyl which is substituted by $-OR^5$ and $-NR^6R^7$, $COOR^4$, $CONR^6R^7$, cycloalkyl which is substituted by OR^5 and $-NR^6R^7$, $COOR^4$, $CONR^6R^7$, or heterocycle which is substituted by OR^5 and $-NR^6R^7$, $COOR^4$, $CONR^6R^7$;

lower alkyl that is substituted by heteroaryl or substituted heteroaryl, and optionally also substituted by halogen, $-OR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, cycloalkyl, heterocycle, cycloalkyl which is substituted by OR^5, $COOR^4$, $CONR^6R^7$, and/or $-NR^6R^7$, and/or heterocycle which is substituted by $-OR^5$, $COOR^4$, $CONR^6R^7$,

and/or -NR^6R^7; and wherein the substituents on the substituted heteroaryl are selected from halogen, -OR^4, -COR^4, -$COOR^4$, NR^6R^7, -SO_2R^4, -$SO_2NR^6R^7$, -NO_2, -CN, -$CONR^6R^7$, lower alkyl, cycloalkyl, heterocycle, lower alkyl which is substituted by -OR^5 -NR^6R^7, $COOR^4$, $CONR^6R^7$, cycloalkyl which is substituted by -OR^5 , -NR^6R^7, $COOR^4$, $CONR^6R^7$, and/or heterocycle which is substituted by -OR^5 , -NR^6R^7, $COOR^4$ and/or $CONR^6R^7$),

aryl (optionally substituted by halogen, -OR^4, -COR^4, -$COOR^4$, -$CONR^6R^7$, lower alkyl, cycloalkyl, heterocycle, lower alkyl which is substituted by -OR^5 , -NR^6R^7, $COOR^4$, $CONR^6R^7$, cycloalkyl which is substituted by -OR^5, $COOR^4$, $CONR^6R^7$, and/or -NR^6R^7, and heterocycle which is substituted by -OR^5, $COOR^4$, $CONR^6R^7$, and/or -NR^6R^7), or

heteroaryl (optionally substituted by halogen, -OR^4, -COR^4, -$COOR^4$, -$CONR^6R^7$, lower alkyl, cycloalkyl, heterocycle, lower alkyl which is substituted by -OR^5, $COOR^4$, $CONR^6R^7$, and/or -NR^6R^7, cycloalkyl which is substituted by -OR^5, $COOR^4$, $CONR^6R^7$, and/or -NR^6R^7, and/or heterocycle which is substituted by -OR^5, $COOR^4$, $CONR^6R^7$, and/or -NR^6R^7).

3. A compound of any one of claims 1 or 2, wherein X is CH and R^3 is lower alkoxy.

4. A compound of any one of claims 1-3 wherein R^1 is lower alkyl substituted by phenyl which is substituted by one to three substituents from the group hydroxy, lower alkoxy, di-(lower alkyl)-amino, di-(lower alkyl)amino-lower alkoxy, morpholino-lower alkyl, carboxy-lower alkoxy and lower alkanoylamino; or R^1 is lower alkyl substituted as before and additionally by hydroxy.

5. A compound of any of claims 1-4, wherein R^1 is lower alkyl substituted by pyridyl, pyrrolyl, N-lower alkyl-pyyrolyl, thienyl, lower-alkoxy substitituted thienyl, furyl, 1,3-benzodioxolyl, or lower-alkoxy substituted 1,3-benzodioxolyl; or R^1 is lower alkyl substituted as before and additionally by hydroxy.

6. A compound of any one of claims 1-3 wherein R^1 is pyridyl.

7. A compound of claim 1 or 2 wherein the optional bond z is present.

8. A compound of claim 4 which is

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(4-methoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (H),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-hydroxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (I),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-methoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (J),

rac-(Z)-4-[3-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]benzoic acid methyl ester (K),

rac-(Z)-4-[3-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]benzoic acid (L),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(2-methoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (M),

rac-(Z)-4-[3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (N),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (O),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(4-hydroxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (Q),

rac-(Z)-1,3-Dihydro-4-[3-(4-dimethylaminophenyl)-3-hydroxy-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (R),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(4-phenoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (S),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-phenyl-1-butynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (T),

rac-(Z)-1,3-Dihydro-4-[3-[4-(3-dimethylaminopropoxy)-phenyl]-3-hydroxy-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (V),

rac-(Z)-1,3-Dihydro-4-[3-(2,3-dimethoxyphenyl)-3-hydroxy-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (EE),

rac-(Z)-1,3-Dihydro-4-[3-(3,4-dimethoxyphenyl)-3-hydroxy-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (FF),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (HH),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-[3-methoxy-4-[2-(4-morpholinyl)-ethoxy]-phenyl]-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (MM),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-[3-methoxy-4-[2-(4-morpholinyl)-ethoxy]-phenyl]-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one hydrochloride salt (NN),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(2,4,5-trimethoxyphenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (PP),

rac-(Z)-[4-[3-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]-2-methoxyphenoxy]acetic acid methyl ester (QQ),

rac-(Z)-[4-[3-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]-2-methoxyphenoxy]acetic acid (RR),

rac-(Z)-4-[3-hydroxy-3-(4-methoxy-1,3-benzodioxol-6-yl)-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (SS),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-[4-[2-(4-morpholinyl)-ethoxy]-phenyl]-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (TT),

rac-(Z)-4-[3-(4-Chloro-2-methylsulfanylmethoxy-phenyl)-3-hydroxy-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (UU),

rac-(Z)-4-[3-(3-Chlorophenyl)-3-hydroxy-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (WW),

rac-(Z)-[4-[3-[2,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]phenoxy]acetic acid 1,1-dimethylethyl ester (XX),

rac-(Z)-[4-[3-[2,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-1-hydroxy-2-propynyl]phenoxy]acetic acid(YY),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-nitrophenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (ZZ),

rac-(Z)-4-[3-(3-Aminophenyl)-3-hydroxy-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (AAA),

rac-(Z)-4-[3-(4-Acetamidophenyl)-3-hydroxy-1-propynyl]-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (BBB), or

rac-(Z)-1,3-Dihydro-4-(3-hydroxy-3-phenyl-1-propynyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (FFF).

9. A compound of claim 5 which is

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-pyridinyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (X),

Synthesis of *rac*-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(1-methyl-pyrrol-2-yl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (AA),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(thiophen-3-yl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (BB),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(1H-pyrrol-2-yl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (DD),*rac*-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(2-pyridinyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (JJ),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(2-thiophenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (KK),

rac-(Z)-1,3-Dihydro-4-[3-hydroxy-3-(3-methoxy-2-thiophenyl)-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (OO), or

rac-(Z)-1,3-Dihydro-4-[3-(2-furanyl)-3-hydroxy-1-propynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (VV).

10. A compound of claim 6 which is

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-[(3-pyridinyl)ethynyl]-2H-indol-2-one (CCC),

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-[(2-pyridinyl)ethynyl]-2H-indol-2-one (DDD),

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-[(4-pyridinyl)ethynyl]-2H-indol-2-one (EEE),

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-4-[(3-pyridinyl)ethynyl]-2H-indol-2-one (GGG),

(Z)-5-Amino-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-[(3-pyridinyl)ethynyl]-2H-indol-2-one (HHH), or

(Z)-N-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-4-[(3-pyridinyl)ethynyl]-1H-indol-5-yl]-2-thiopheneacetamide (III).

11. A compound of claim 1 which is

4-[(E)-2-(2-Chlorophenyl)-ethenyl]-1,3-dihydro-(Z)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (KKK),

1,3-Dihydro-(Z)-3-[(1H-pyrrol-2yl)methylene]-[(E)-2-phenylethenyl]-2H-indol-2-one (LLL),

1,3-Dihydro-(Z)-3-[(3-methoxy-1H-pyrrol-2yl)methylene]-[(E)-2-phenylethenyl]-2H-indol-2-one (MMM),

1,3-Dihydro-4-[(E)-2-(4-methoxyphenyl)-ethenyl]-(Z)-3-[(1H-pyrrol-2-yl)methlene]-2H-indol-2-one (NNN),

1,3-Dihydro-(Z)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-[(E)-2-(4-methoxy-phenyl)-ethenyl]-2H-indol-2-one (OOO),

4-[(E)-2-[2,3-Dihydro-(Z)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]ethenyl]benzoic acid methyl ester (PPP), or

1,3-Dihydro-4-[(E)-2-(3,4-dimethoxyphenyl)-ethenyl]-(Z)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (QQQ).

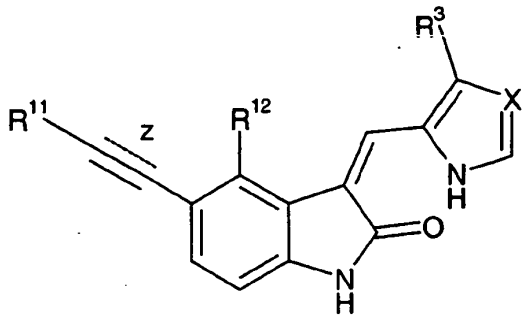
12. Acompound of claim 1, which is

(Z)-1,3-Dihydro-4-(phenylethynyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (D),

(Z)-1,3-Dihydro-4-[(4-methoxyphenyl)ethynyl]-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (G) or

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-(3-phenoxy-1-propynyl)-2H-indol-2-one (Y).

13. A compound having the formula:



II

and the pharmaceutically acceptable salts thereof,

wherein:

R^{11} is hydrogen, $-COR^4$, $-COOR^4$, $-CONR^6R^7$,

lower alkyl (optionally substituted by $-OR^5$, $-NR^6R^7$, halogen, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, cycloalkyl, heterocycle, aryl, and/or heteroaryl),

cycloalkyl (optionally substituted by $-OR^5$, $-NR^6R^7$, halogen, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, lower alkyl, heterocycle, aryl, and/or heteroaryl)

heterocycle (optionally substituted by $-OR^5$, $-NR^6R^7$, halogen, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, lower alkyl, cycloalkyl, aryl, and/or heteroaryl),

aryl (optionally substituted by the group consisting of $-OR^5$, $-NR^6R^7$, halogen, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, lower alkyl, and/or perfluoroalkyl) or

heteroaryl (optionally substituted by $-OR^5$, $-NR^6R^7$, halogen, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$, -CN, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, lower alkyl, and/or perfluoroalkyl);

R^{12} is hydrogen, $-OR^4$, $-OCOR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-NR^6R^7$, halogen, $-NO_2$, -CN, $-SO_2R^4$, $-SO_2NR^6R7$, perfluoroalkyl,

lower alkyl (optionally substituted by OR^4, $-NR^6R^7$, cycloalkyl, heterocycle, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and/or halogen),

cycloalkyl (optionally substituted by $-OR^4$, $-NR^6R^7$, lower alkyl, heterocycle, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and/or halogen), or

heterocycle (optionally substituted by $-OR^4$, $-NR^6R^7$, lower alkyl, cycloalkyl, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and/or halogen), and

R^3 through R^7, X and z are as defined for formula I in claim 1.

14. A compound of claim 1 or 13, wherein

R^4 is hydrogen, lower alkyl (optionally substituted by (a), cycloalkyl and /or heterocycle), cycloalkyl (optionally substituted by (a), lower alkyl and/or heterocycle), or heterocycle (optionally substituted by (a), lower alkyl and/or cycloalkyl), where (a) is $-OR^5$, $-COOR^8$, $-COR^8$, $-CONR^8R^9$, $-NR^6R^7$, -CN, $-NO_2$, $-SO_2R^8$, and/or $-SO_2NR^8R^9$; and R^5 is hydrogen, $-COR^8$, $-CONR^8R^9$ or lower alkyl (optionally substituted by $-OR^9$, $-NR^9R^{10}$, $-N(COR^9)R^{10}$, $-COR^9$, $-CONR^9R^{10}$ and/or $-COOR^9$); and R^1, R^2, R^3, R^8, R^9, R^{10}, X and z are as in claim 1.

15. A compound of claim 13 wherein

R^3 is hydrogen, $-OR^4$, $-NR^6R^7$, and/or lower alkyl (optionally substituted by $-OR^8$ and/or $-NR^6R^7$);

R^4 is hydrogen, lower alkyl (optionally substituted by one or more $-OR^5$, $-COOR^8$, $-COR^8$, $-CONR^8R^9$), cycloalkyl (optionally substituted by one or more $-OR^5$, $-COOR^8$, $-COR^8$ and $-CONR^8R^9$), or heterocycle (optionally substituted by one or more $-OR^5$, $-COOR^8$, $-COR^8$ and $-CONR^8R^9$);

R^5 is hydrogen, $-COR^8$, $-CONR^8R^9$, or lower alkyl;

R^6 and R^7 are each independently hydrogen, $-COR^8$, $-COOR^8$, $-CONR^8R^9$, or lower alkyl (optionally substituted by one or more of $-OR^9$, $-NR^8R^9$, $COOR^8$, and $CONR^8R^9$), or

alternatively, $-NR^6R^7$ optionally form a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms and being optionally substituted by one or more of lower alkyl, $-OR^5$, $-COR^8$, $-COOR^8$, $-CONR^8R^9$, and $-NR^5R^9$;

R^8 is hydrogen or lower alkyl (optionally substituted by one or more of aryl, heteroaryl, $-OR^9$, $COOR^9$, $CONR^9R^{10}$, and $-NR^9R^{10}$);

R^{11} is aryl (optionally substituted by $-OR^5$ and/or $-NR^6R^7$);

R^{12} is hydrogen, $-COR^4$, $-COOR^4$, $-CONR^6R^7$,

lower alkyl (optionally substituted by one or more of $-OR^4$, $-NR^6R^7$, cycloalkyl, heterocycle, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and halogen),

cycloalkyl (optionally substituted by one or more of $-OR^4$, $-NR^6R^7$, lower alkyl, heterocycle, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and halogen), or

heterocycle (optionally substituted by one or more of $-OR^4$, $-NR^6R^7$, lower alkyl, cycloalkyl, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, -CN, $-NO_2$, $-SO_2R^4$, $-SO_2NR^6R^7$ and halogen);

and the optional bond z is present.

16. A compound of claim 13 which is

(Z)-1,3-Dihydro-5-ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (SSS),

(Z)-1,3-Dihydro-5-(4-hydroxyphenyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (TTT),

(Z)-1,3-Dihydro-5-(3-nitrophenyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (UUU),

(Z)-1,3-Dihydro-5-phenylethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (VVV),

(Z)-1,3-Dihydro-5-(3-hydroxyphenyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (WWW),

(Z)-1,3-Dihydro-5-(2-nitrophenyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (XXX),

(Z)-1,3-Dihydro-5-(4-nitrophenyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (ZZZ),

(Z)-5-(4-Aminophenyl)ethynyl-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (AAAA),

(Z)-1,3-Dihydro-5-ethynyl-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one (DDDD),

(Z)-1,3-Dihydro-5-(3-pyridinyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (EEEE),

(Z)-1,3-Dihydro-5-(2-pyridinyl)ethynyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one (FFFF),

(Z)-1,3-Dihydro-5-(4-hydroxyphenyl)ethynyl-3-[(3-methoxy-1H-pyrrol-2-yl)-methylene]-2H-indol-2-one (GGGG),

(Z)-1,3-Dihydro-5-(4-methoxyphenyl)ethynyl-3-[(1H-pyrrol-2-yl)-methylene]-2H-indol-2-one (HHHH),

(Z)-1,3-Dihydro-3-[(1H-pyrrol-2-yl)-methylene]-5-(2-thiophenyl)ethynyl-2H-indol-2-one (IIII), or

(Z)-1,3-Dihydro-5-ethynyl-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one, trifluoroacetate salt (LLLL).

17. The compounds

1,3-Dihydro-5-fluoro-4-iodo-2H-indol-2-one,

(Z)-1,3-Dihydro-3-[(1H-pyrrol-2-yl)methylene]-5-(trimethylsilyl)ethynyl-2H-indol-2-one,

(Z)-5-Bromo-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one,

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-(trimethylsilyl)ethynyl-2H-indol-2-one,

(Z)-5-Bromo-1,3-dihydro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one,

(Z)-1,3-Dihydro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-5-(trimethylsilyl)ethynyl-2H-indol-2-one.

18. A pharmaceutical composition comprising as an active ingredient a compound of claim 1 or 13 and a pharmaceutically acceptable carrier or excipient.

19. The compounds of claim 1 and 13 for use as medicaments.

20. The use of a compound of claim 1 or 13 or prodrugs and pharmaceutically active metabolites of such compound in the preparation of a medicament for the treatment or control of inflammatory diseases, particularly rheumatoid arthritis.

21. The novel compounds, compositions and use as described hereinbefore, especially with reference to the Examples.